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Phosphoisoquinolines

First Synthesis of (*R*)- and (*S*)-1,2,3,4-Tetrahydroisoquinoline-3-phosphonic Acid (Tic^P) Using a Pictet–Spengler Reaction

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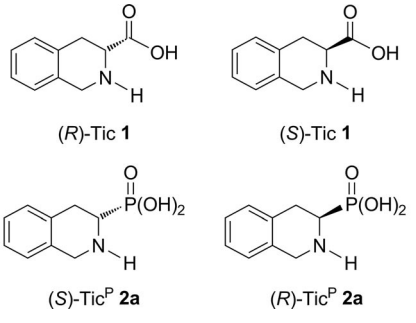
Abstract: We report here a practical and efficient synthesis of diethyl 1,2,3,4-tetrahydroisoquinoline-3-phosphonate derivatives. The target compounds were prepared in good yield using a Pictet–Spengler reaction involving α-amino phosphonates that were easily obtained. We have paid special attention to the synthesis of (*R*)- and (*S*)-1,2,3,4-tetrahydroisoquinoline-3-phosphonic acid (Tic^P) **2a**, a conformationally constrained analogue of phosphophenylalanine Phe^P. The procedure is based on the preparation of racemic phosphophenylalanine (Phe^P) diethyl ester followed by chiral chromatographic separation and subsequent Pictet–Spengler chemistry.

Introduction

The 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) **1**, considered a conformationally constrained analogue of phenylalanine (Phe) with a fused phenyl ring, is an important non-natural α-amino acid often used as a key intermediate in organic synthesis for the preparation of biologically active compounds. Possibly one of the most successful examples of such applications of **1** has involved its use as a proline replacement in the drug enalapril. This modification led to quinapril, a newly approved angiotensin converting enzyme (ACE) inhibitor.[1] This discovery led to the preparation of several pharmacologically relevant compounds that have been evaluated as anti-thrombotic agents,[2] inhibitors of P-glycoprotein,[3] matrix-metalloproteinase inhibitors,[4] hepatitis C virus NS3 protease inhibitors,[5] and as Rev-ErbA agonists.[6] Such agents have also been tested as inhibitors of aminopeptidase N (APN/CD13) and MMP-2,[7] as analogues of the antimicrobial gramicidin S,[8] as opioid pharmacophores,[9] and as potent Rho Kinase inhibitors. Agents containing **1** and related congeners are thus considered promising drug leads in the development of treatments for many diseases including hypertension, multiple sclerosis, cancer and glaucoma.[10] Furthermore, Tic **1** has been used as a precursor in the synthesis of several catalysts[11] and chiral hydrides.[12]

Due to the important properties exhibited by Tic **1** and related derivatives, much effort has been dedicated to the preparation of these compounds, mainly through the use of Pictet–Spengler reactions.[13,14] However, the synthesis of the **1** analogue 1,2,3,4-tetrahydroisoquinoline-3-phosphonic acid (Tic^P) **2a** from racemic or enantiomerically pure phosphophenylalanine Phe^P diethyl ester using Pictet–Spengler chemistry has not, to the best of our knowledge, been described in the literature. This is somewhat surprising due to the great promise this compound likely has in medicinal chemistry and organic synthesis as is demonstrated by the well-established significance of α-amino phosphonic acids and their derivatives.[15,16] Consequently, there is great interest and importance in developing new methods for the preparation of compound **2a** and related agents.[17]



Considering the high value of these non-coded compounds in connection with our current research interest in the synthesis of novel conformationally restricted α-amino phosphonic acids,[18] we report herein the first convenient synthesis of enantiomerically pure (*R*)- and (*S*)-1,2,3,4-tetrahydroisoquinoline-3-phosphonic acid (Tic^P) **2a**. The procedure is based on the preparation of racemic phosphophenylalanine Phe^P diethyl ester followed by chiral chromatography and subsequent Pictet–Spengler chemistry.

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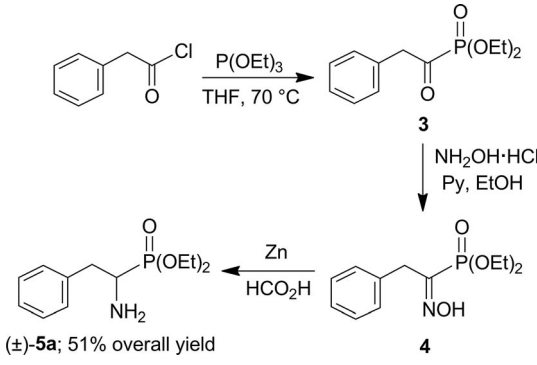
Results and Discussion

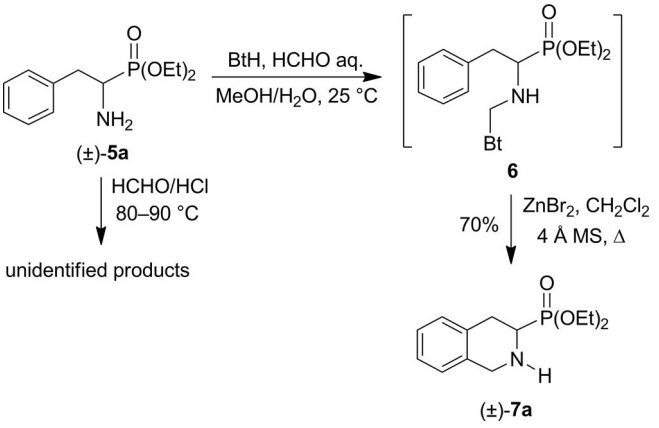
For the synthesis of target compound **2a**, our synthetic sequence begins with the preparation of diethyl phosphophenylalaninate (±)-**5a**. For this aim, we explored the application of methods already described in the literature.[19] Thus, commercially available phenylacetyl chloride was treated with triethyl phosphite at 70 °C to afford α-keto phosphonate **3**, which without additional purification was treated with hydroxylamine hydrochloride and pyridine in ethanol, to render the corresponding oxime **4**. Reduction of oxime **4** with zinc in formic acid at room temperature, provided diethyl phosphophenylalaninate (±)-**5a** in 51 % overall yield (Scheme 1).



Scheme 1. Preparation of diethyl phosphophenylalaninate (±)-**5a**.

With diethyl phosphophenylalaninate (±)-**5a** in hand, and applying the well-established protocol for the synthesis of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (Tic) **1** under Pictet–Spengler conditions,[14] we carried out the reaction of (±)-**5a** with formaldehyde in the presence of 37 % HCl. However, after several attempts, only a complex mixture of unidentified products was obtained, possible due to hydrolysis of the phosphonate group. On the other hand, it has also been reported that Tic **1** can be obtained using a benzotriazole-assisted methodology. With this background, and applying a procedure described by Katritzky and co-workers,[20] diethyl phosphophenylalaninate (±)-**5a**, benzotriazole (BtH) and formaldehyde were allowed to react at room temperature, rendering *N*-[(benzotriazolyl)methyl] intermediate **6**. Compound **6**, without additional purification, was treated with aluminum chloride in dichloromethane under refluxing conditions in efforts to generate the desired product (±)-**7a**. However, under these conditions, only decomposition products were obtained. Alternatively, the reaction of intermediate **6** with $ZnBr_2$ in the presence of 4 Å molecular sieves in dichloromethane at reflux, provided the desired compound (±)-**7a** in 70 % yield (Scheme 2).

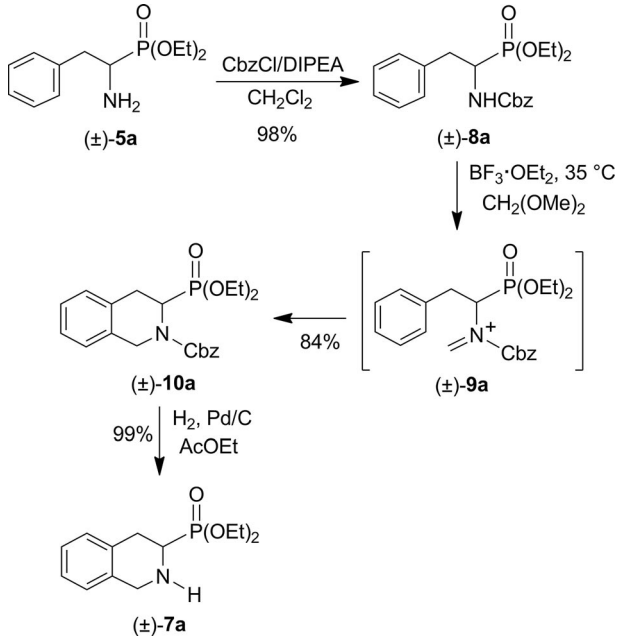
With this procedure, the synthesis of our target molecule (±)-**7a** was achieved. However, this approach was deemed impractical for larger-scale reactions since several by-products were obtained and purification proved difficult. To resolve this problem in a general way, an electron-withdrawing group, specifically benzyloxycarbonyl (Cbz), was incorporated by way of *N*-protection to produce the *N*-acyliminium ion, anticipated to be amenable to Pictet–Spengler cyclization.[21] Additionally, we changed the formaldehyde source to that of more reactive dimethoxymethane, which served both as solvent as well as the



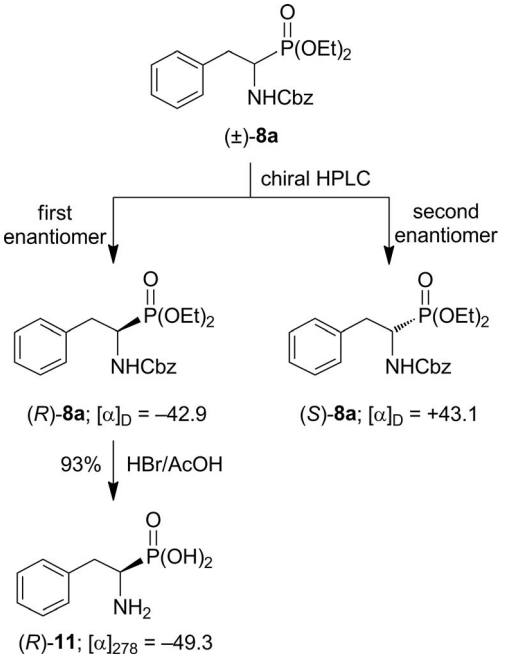
Scheme 2. Synthesis of compound (±)-**7a**.

formaldehyde source. We envisioned that catalysis by $BF_3{\cdot}OEt_2$, would mediate the formation of formaldehyde from dimethoxymethane, thus facilitating the desired Pictet–Spengler cyclization.[22] Therefore, diethyl phosphophenylalaninate (±)-**5a** was treated with benzyloxycarbonyl chloride and *N*,*N*-diisopropylethylamine (DIPEA) in dichloromethane to afford *N*-Cbz-protected α-amino phosphonate (±)-**8a** in 98 % yield. Reaction of (±)-**8a** with dimethoxymethane at 35 °C in the presence of catalytic $BF_3{\cdot}OEt_2$, gave *N*-Cbz-protected diethyl 1,2,3,4-tetrahydroisoquinoline-3-phosphonate (±)-**10a** in 84 % yield, through the agency of *N*-acyliminium species (±)-**9a**. When the reaction was carried out at room temperature, low yields were observed, and at temperatures higher than 35 °C, several unidentified products were formed, indicating that the temperature was a critical factor in this reaction. Cleavage of the *N*-Cbz group in compound (±)-**10a** was accomplished by hydrogenolysis in the presence of Pd/C as catalyst in ethyl acetate to render diethyl 1,2,3,4-tetrahydroisoquinoline-3-phosphonate (±)-**7a** in 99 % yield. Importantly, this procedure enabled the preparation of (±)-**7a** in large quantities (Scheme 3).

With these results, the next step was to explore the scope of the Pictet–Spengler reaction using enantiomerically pure (*R*)- and (*S*)-phosphophenylalanine diethyl ester **8a** in order to obtain the (*R*)- and (*S*)-1,2,3,4-tetrahydroisoquinoline-3-phosphonic acid (Tic^P) **2a** in optically pure form. Moreover, this would enable us to test the configurational stability of enantiomerically pure α-amino phosphonates **8a** and **10a** in this reaction. To achieve this goal, we prepared enantiomerically pure compounds (*R*)- and (*S*)-**8a**. Although these compounds have been obtained by asymmetric synthesis methods,[17b,17e] and using chemical and biocatalytic resolutions,[23] to the best of our knowledge, preparative chiral HPLC resolution of racemic phosphophenylalanine derivatives has not been explored.[24] Based on our previous experience in the preparative-scale chiral HPLC resolution of protected amino acids and α-amino phosphonates,[25] we addressed the chromatographic resolution of racemate **8a** using commercially available preparative columns Chiralpak® IA,[26a] IB[26b] and IC.[26c] These columns contain stationary phases based on polysaccharide chiral supports covalently bonded to a silica gel matrix, which provide excellent chiral recognition, high loading capacity and are very stable in



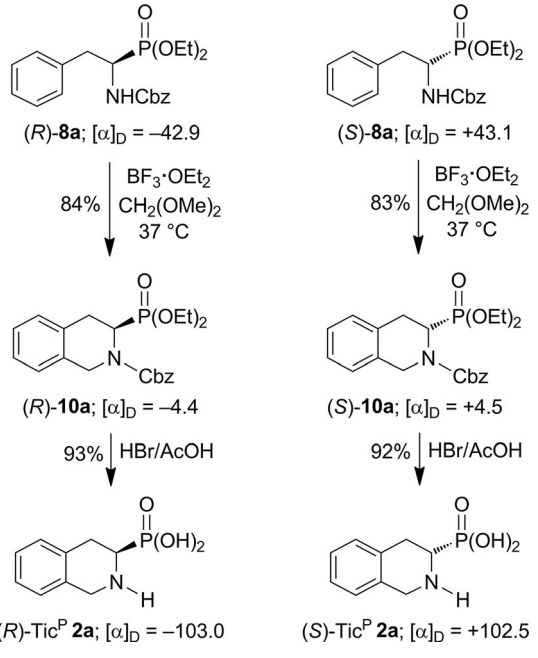
Scheme 3. Synthesis of (±)-**7a** through the agency of intermediate *N*-acyliminium species (±)-**9a**.



Scheme 4. HPLC resolution of racemic phosphophenylalanine derivative **8a**.

the presence of a wide range of organic solvents.[26–28] In order to establish the appropriate conditions for the preparative resolution of compound (±)-**8a**, we first tested the separation at the analytical level using 250 × 4.6 mm ID Chiralpak® IA, IB and IC columns. No resolution was observed using the Chiralpak® IB column, and with the Chiralpak® IC column only very poor enantiodiscrimination was obtained. However, assays performed on the Chiralpak® IA column showed suitable separation of both enantiomers. The best separation conditions were found using *n*-hexane/*i*PrOH (85:15) as the mobile phase at a flow rate of 1 mL/min. The addition of a third solvent to the mobile phase (acetone, chloroform and *tert*-butyl methyl ether) did not improve the enantioseparation. The analytical conditions were used working in overload mode and then scaled-up for the preparative resolution of (±)-**8a** using a 250 × 20 mm ID Chiralpak® IA column. The resolution was achieved by successive injections of a solution of (±)-**8a** in chloroform (0.80 g per mL of solvent) to obtain about 1.0 g of each enantiomer in a single passage of the racemate through the column. The enantiomeric purities of the resolved materials were evaluated on an analytical scale. The absolute configurations of (*R*)- and (*S*)-**8a** were assigned on the basis of optical rotation data and comparisons with previously reported data (Scheme 4).[29] Additionally, treatment of compound (*R*)-**8a** with a 33 % solution of HBr in acetic acid followed by purification using an ion-exchange column, afforded (*R*)-phosphophenylalanine **11** in almost quantitative yield. Comparison of the specific optical rotation of (*R*)-**11** with established data in the literature confirmed the absolute configuration assignments.[30]

With (*R*)- and (*S*)-phosphophenylalanine diethyl esters **8a** in enantiomerically pure form in hand, the next step was the synthesis of our target molecules. For this purpose, and based on our research on the Pictet–Spengler reaction with racemic **8a**, we carried out the reaction of (*R*)-**8a** with dimethoxymethane at 37 °C in the presence of catalytic BF_3·OEt_2, to produce diethyl (*R*)-1,2,3,4-tetrahydroisoquinoline-3-phosphonate (*R*)-**10a** in 84 % yield. Treatment of (*R*)-**10a** with a 33 % solution of HBr in acetic acid at room temperature produced (*R*)-1,2,3,4-tetrahydroisoquinoline-3-phosphonic acid (Tic^P) (*R*)-**2a** in 93 % yield. Under identical conditions (*S*)-**8a** was converted into (*S*)-1,2,3,4-tetrahydroisoquinoline-3-phosphonic acid (*S*)-**2a** in excellent yield (Scheme 5).

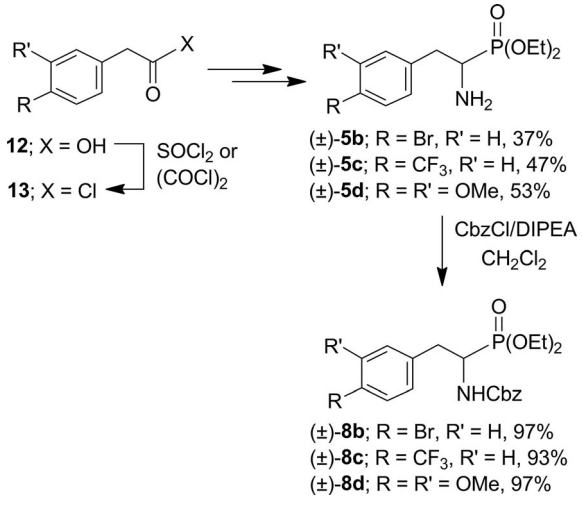


Scheme 5. Synthesis of the target compounds (*R*)-**2a** and (*S*)-**2a**.

Finally, analyses of racemate (±)-**10a** and both enantiomers (*R*)- and (*S*)-**10a** using a 150 × 4.6 mm ID Chiralpak® IB column

and *n*-hexane/*i*PrOH (90:10) as the mobile phase at a flow rate of 1 mL/min, revealed that the Pictet–Spengler reaction proceeded without racemization, establishing the configurational stability of **8a** and **10a** under these reaction conditions.

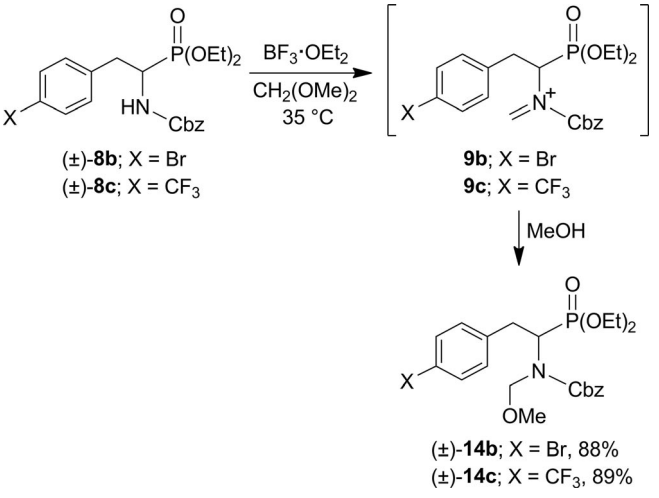
To explore the scope of this method for the synthesis of diethyl 1,2,3,4-tetrahydroisoquinoline-3-phosphonates, several β-aryl-substituted α-amino phosphonates were examined in detail. β-Aryl-substituted α-amino phosphonates (±)-**5b**–**d** and *N*-Cbz-protected derivatives (±)-**8b**–**d** were prepared in moderate to excellent yields from the corresponding arylacetic acids **12** via their acyl chlorides **13** according to the procedure described above (Scheme 6).



Scheme 6. Synthesis of (±)-**5b**–**d** and their protected derivatives (±)-**8b**–**d**.

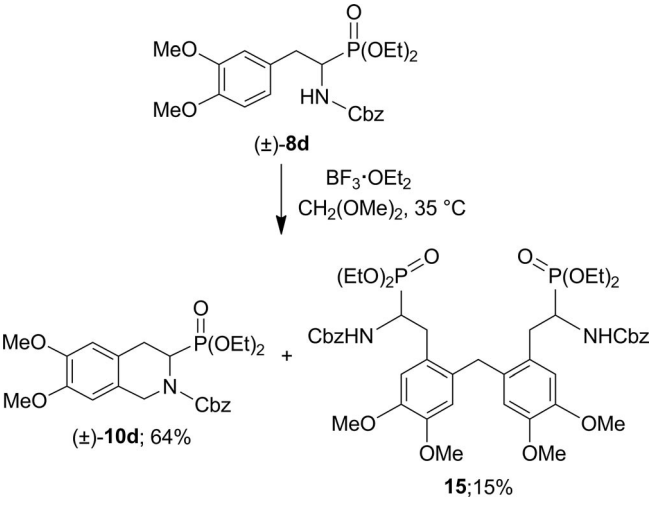
With the α-amino phosphonates (±)-**8b**–**d** in hand, we started with the reaction of *N*-Cbz-protected diethyl (4-bromophenyl)phosphoalaninate (±)-**8b** and dimethoxymethane in the presence of catalytic BF_3·OEt_2 at 35 °C; under these conditions, the desired 1,2,3,4-tetrahydroisoquinoline-3-phosphonate was not isolated. Instead, this reaction produced *N*-methoxymethyl derivative (±)-**14b** in 88 % yield. Similar results were obtained when the *N*-Cbz-protected diethyl [4-(trifluoromethyl)phenyl]phosphoalaninate (±)-**8c** was allowed to react under the same conditions to render (±)-**14c** in 89 %. Compounds (±)-**14b** and (±)-**14c** were fully characterized by NMR spectroscopy and mass spectrometry and, partly on this basis, we propose that iminium ions **9b** and **9c** were formed. However, it is likely that the insufficient reactivity of the aromatic ring with electron-withdrawing substituents, enables these species (**9b**,**c**) to react with methanol, thus leading to the formation of (±)-**14b** and (±)-**14c** (Scheme 7).[31]

With these results, we next turned our attention to the Pictet–Spengler reaction of *N*-Cbz-protected diethyl (3,4-dimethoxyphenyl)phosphoalaninate (±)-**8d** with dimethoxymethane and catalytic BF_3·OEt_2 at 35 °C. These reaction conditions generated the expected product (±)-**10d** in 64 % yield and a dimeric product **15** in 15 % yield (Scheme 8). On the basis of these data, it is clear that the cyclization event in the Pictet–Spengler reaction proceeds optimally when the ring-closure position is activated by an electron-donating substituent. It is also known that activation in such reactions may confer hydroxy-



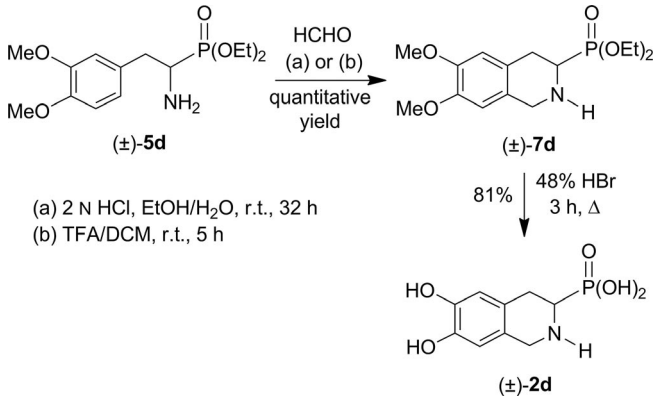
Scheme 7. Synthesis of the *N*-methoxymethyl derivatives (±)-**14b** and **14c**.

methylation of the aromatic ring, thus enabling the formation of bis(aryl)methylenes, trimers and cyclotetramers;[21b] these observations effectively support the legitimacy of our observations with this reaction and set of reactants.



Scheme 8. Synthesis of (±)-**10d** and dimeric product **15**.

In order to equilibrate the reactivity of the aromatic ring and the nitrogen atom, we next performed the Pictet–Spengler reaction of diethyl (3,4-dimethoxyphenyl)phosphoalaninate (±)-**5d** with excess of formaldehyde in the presence of 2 N HCl (1 equiv.) at room temperature for 32 h. These conditions afforded diethyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-phosphonate (±)-**7d** in quantitative yield. Compound (±)-**7d** was also obtained in quantitative yield by reaction of (±)-**5d** with formaldehyde and excess of trifluoroacetic acid (TFA) in dichloromethane at room temperature for 5 h.[32] Hydrolysis of the phosphonate moiety with simultaneous O–Me bond cleavage in compound (±)-**7d** was carried out in refluxing concd. HBr to furnish 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-phosphonic acid (±)-**2d** in 81 % yield, a conformationally constrained L-DOPA^P analogue (Scheme 9).



Scheme 9. Synthesis of the cyclic DOPA^{P} analogue (±)-**2d**.

Conclusions

We have developed, for the first time, a practical and efficient synthesis of diethyl 1,2,3,4-tetrahydroisoquinoline-3-phosphonates from α-amino phosphonates using the Pictet–Spengler reaction. This report highlights the use of α-amino phosphonates as key intermediates in the Pictet–Spengler reaction. One application of this procedure involves the synthesis of enantiomerically pure (*R*)- and (*S*)-1,2,3,4-tetrahydroisoquinoline-3-phosphonic acid (Tic^{P}) **2a** from diethyl phenylphosphoalaninate **8a** which is readily obtained (on a large scale) by chiral HPLC separations. Additionally, the configurational stabilities of starting materials and products were evaluated.

Experimental Section

General: All reagents were used as received from commercial suppliers without further purification. Thin-layer chromatography (TLC) was performed on Macherey–Nagel Polygram® SIL G/UV$_{254}$ precoated silica gel polyester plates. The products were visualized by exposure to UV light (254 nm), iodine vapors or submersion in a solution of phosphomolybdic acid in ethanol. Flash chromatography was performed using Silica 60 M (0.04–0.063 mm, 230–400 mesh) from Macherey–Nagel. Melting points were determined with a Gallenkamp apparatus and are uncorrected. IR spectra were registered using a Nicolet Avatar 360 FTIR spectrophotometer; $\tilde{\nu}_{max}$ is given for the main absorption bands. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded with Bruker AV-400 or AV-300 instruments at room temperature except when another temperature is specified; the residual solvent signal was used as the internal standard (^{1}H and ^{13}C) or H_3PO_4 (^{31}P, internal); chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (*J*) in Hertz. High Resolution Mass Spectra (HRMS) were obtained with a Bruker Microtof-Q spectrometer.

High-Performance Liquid Chromatography: HPLC was carried out with a Waters 600 HPLC system equipped with a 2996 photodiode array detector or a Hewlett–Packard 1100 system equipped with a VIS-UV detector (used at the analytical level) and a 2487 dual-wavelength absorbance detector (used for the preparative-scale resolution). Analytical assays were performed using 250 × 4.6 mm Chiralpak® IA, IB, and IC columns (Daicel Chemical Industries Ltd., Japan), eluting with different binary and ternary mixtures at flow rates ranging from 0.8 to 1.0 mL/min. The preparative resolution was carried out using 250 × 20 mm Chiralpak® IA columns and eluting with *n*-hexane/*i*PrOH (85:15) at a flow rate of 18 mL/min. The process was monitored by UV absorption at 220 nm.

General Procedure for the Synthesis of α-Amino Phosphonates 5a–d: Thionyl chloride (8.3 g, 5.1 mL, 69.1 mmol) was added dropwise to a solution of (4-bromophenyl)acetic acid (5.0 g, 23.3 mmol), dichloromethane (5 mL) and *N*,*N*-dimethylformamide (0.15 mL). The resulting solution was stirred at room temperature in a well-ventilated hood overnight. The reaction mixture was concentrated in vacuo to give the crude (4-bromophenyl)acetyl chloride as a yellow liquid. The crude acyl chloride was dissolved in tetrahydrofuran (13 mL), cooled to 0 °C, and triethyl phosphite (3.86 g, 4.1 mL, 23.3 mmol) was added dropwise under anhydrous conditions. When the addition was complete, the solution was warmed at 70 °C and stirred for additional 15 min. The volatile compounds were evaporated in vacuo to obtain the α-keto phosphonate, which was added to a solution of hydroxylamine hydrochloride (1.94 g, 28 mmol) in dry pyridine (4.2 mL) and ethanol (7 mL). The reaction mixture was stirred at room temperature for 12 h and then concentrated in vacuo. The crude product was dissolved in dichloromethane (40 mL), washed with 3 N HCl (2 × 10 mL) and water (10 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo to obtain the crude oxime. Finally, the crude oxime under argon was added to a suspension of zinc (6.1 g, 93.3 mmol) in formic acid (23.2 mL), and the mixture was stirred at room temperature overnight. The suspension was filtered, and the filtrate was concentrated in vacuo to provide the crude product, which was purified by flash chromatography using AcOEt/MeOH (95:5) to give compound **5b** (2.86 g, 37 %) as a yellow oil. Spectroscopic data for **5a**[33] and **5b**[34] were identical to those reported in the literature.

Diethyl [1-Amino-2-(4-trifluoromethylphenyl)ethyl]phosphonate (5c): According to the general procedure, compound **5c** was obtained (1.49 g, 47 % yield) from [4-(trifluoromethyl)phenyl]acetic acid (2.0 g, 9.8 mmol) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3378, 3300, 1239, 1066, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 1.32 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 1.38 (br. s, 2 H, NH_2), 2.69–2.77 (m, 1 H, CH_2CH), 3.18–3.27 (m, 2 H, CH_2CH, CHP), 4.10–4.18 (m, 4 H, OCH_2CH_3), 7.34 (d, *J* = 8.0 Hz, 2 H, H_{arom}), 7.54 (d, *J* = 8.0 Hz, 2 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (d, *J* = 5.6 Hz, CH_3CH_2O), 37.7 (CH_2CH), 50.2 (d, *J* = 152.9 Hz, CHP), 62.4 (d, *J* = 7.5 Hz, OCH_2CH_3), 62.5 (d, *J* = 7.5 Hz, OCH_2CH_3), 124.3 (q, *J* = 271.8 Hz, CF_3), 125.5 (q, *J* = 3.8 Hz), 129.1 (q, *J* = 32.5 Hz), 129.7, 142.3 (d, *J* = 15.4 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.48 ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –62.47 ppm. HRMS (ESI): calcd. for $C_{13}H_{20}F_3NO_3P$ $[M + H]^+$ 326.1133; found 326.1135.

Diethyl [1-Amino-2-(3,4-dimethoxyphenyl)ethyl]phosphonate (5d): According to the general procedure, compound **5d** was obtained (10.35 g, 53 % yield) from (3,4-dimethoxyphenyl)acetic acid (12.0 g, 61.2 mmol) as a white solid. M.p. 58–59 °C. IR (neat): $\tilde{\nu}$ = 3378, 3297, 1231, 1057, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 6 H, CH_3CH_2O), 1.48 (br. s, 2 H, NH_2), 2.58 (ddd, *J* = 13.9, 11.0, 8.8 Hz, 1 H, CH_2CH), 3.15 (ddd, *J* = 13.8, 6.9, 3.3 Hz, 1 H, CH_2CH), 3.19–3.26 (m, 1 H, CHP), 3.83 (s, 3 H, CH_3O), 3.84 (s, 3 H, CH_3O), 4.20–4.11 (m, 4 H, OCH_2CH_3), 6.81–6.71 (m, 3 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (d, *J* = 5.5 Hz, CH_3CH_2O), 37.4 (CH_2CH), 50.4 (d, *J* = 153.9 Hz, CHP), 55.9 (CH_3O), 55.9 (CH_3O), 62.3 (d, *J* = 6.8 Hz, OCH_2CH_3), 62.4 (d, *J* = 7.0 Hz, OCH_2CH_3), 111.3, 112.2, 121.3, 130.3 (d, *J* = 16.4 Hz), 147.9, 149.1 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.12 ppm. HRMS (ESI): calcd. for $C_{14}H_{25}NO_5P$ $[M + H]^+$ 318.1470; found 318.1445.

General Procedure for the Synthesis of *N*-Cbz-α-Amino Phosphonates 8a–d: Benzyloxycarbonyl chloride (2.52 g, 2.2 mL, 14.8 mmol) was added dropwise under argon to a solution of com-

pound **5a** (1.9 g, 7.4 mmol) and *N*,*N*-diisopropylethylamine (3.82 g, 5.2 mL, 29.6 mmol) in dichloromethane (37 mL) at 0 °C. The resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with dichloromethane (30 mL), washed with 1 N HCl (30 mL), water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo, and the crude product was purified by flash chromatography using AcOEt/hexane (70:30) to afford compound **8a** (2.83 g, 98 % yield) as a white solid. **8a** and **8b** were identical to those reported in the literature.[29]

Diethyl {1-[(Benzyloxycarbonyl)amino]-2-[4-(trifluoromethyl)-phenyl)]ethyl}phosphonate (8c): According to the general procedure, a mixture of compound **5c** (1.0 g, 3.07 mmol), dichloromethane (15.5 mL), *N*,*N*-diisopropylethylamine (1.59 g, 2.2 mL, 12.3 mmol) and benzyloxycarbonyl chloride (1.05 g, 0.88 mL, 6.15 mmol) was allowed to react to give **8c** (1.31 g, 93 % yield) as a white solid. M.p. 82–84 °C. IR (neat): $\tilde{\nu}$ = 3259, 1712, 1264, 1057, 1032 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 1.28 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 2.88–3.00 (m, 1 H, CH_2CH), 3.20–3.29 (m, 1 H, CH_2CH), 3.99–4.17 (m, 4 H, OCH_2CH_3), 4.32–4.47 (m, 1 H, CHP), 5.00 (s, 2 H, OCH_2Ph), 5.46 (d, *J* = 9.9 Hz, 1 H, NH), 7.18–7.25 (m, 2 H, H_{arom}), 7.26–7.32 (m, 3 H, H_{arom}), 7.34 (d, *J* = 7.8 Hz, 2 H, H_{arom}), 7.50 (d, *J* = 7.8 Hz, 2 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (d, *J* = 5.7 Hz, CH_3CH_2O), 35.9 (d, *J* = 3.8 Hz, CH_2CH), 48.5 (d, *J* = 157.4 Hz, CHP), 62.8 (d, *J* = 6.7 Hz, OCH_2CH_3), 63.1 (d, *J* = 7.1 Hz, OCH_2CH_3), 67.2 (OCH_2Ph), 124.3 (q, *J* = 272.1 Hz, CF_3), 125.4 (q, *J* = 3.7 Hz), 128.1, 128.3, 128.6, 129.2 (q, *J* = 32.3 Hz), 129.7, 136.3, 141.0 (d, *J* = 13.3 Hz), 155.9 (d, *J* = 7.1 Hz, C=O) ppm. ^{31}P NMR (162 MHz, $CDCl_3$, asterisk denotes minor rotamer): δ = 23.00*, 23.55 ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –62.37 ppm. HRMS (ESI): calcd. for $C_{21}H_{26}F_3NO_5P$ $[M + H]^+$ 460.1501; found 460.1469.

Diethyl {1-[(*N*-Benzyloxycarbonyl)amino]-2-(3,4-dimethoxy-phenyl)ethyl}phosphonate (8d): According to the general procedure, a mixture of compound **5d** (1.0 g, 3.15 mmol), dichloromethane (16 mL), *N*,*N*-diisopropylethylamine (1.63 g, 2.2 mL, 12.6 mmol) and benzyloxycarbonyl chloride (1.08 g, 0.9 mL, 6.33 mmol) was allowed to react to give compound **8d** (1.33 g, 93 % yield) as a white solid. M.p. 89–91 °C. IR (neat): $\tilde{\nu}$ = 3244, 1715, 1256, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 1.28 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 2.74–2.87 (m, 1 H, CH_2CH), 3.11–3.22 (m, 1 H, CH_2CH), 3.79 (s, 3 H, OCH_3), 3.83 (s, 3 H, CH_3O), 3.98–4.15 (m, 4 H, OCH_2CH_3), 4.30–4.44 (m, 1 H, CHP), 4.99 (s, 2 H, OCH_2Ph), 5.20 (d, *J* = 10.2 Hz, 1 H, NH), 6.68–6.78 (m, 3 H, H_{arom}), 7.16–7.22 (m, 2 H, H_{arom}), 7.26–7.32 (m, 3 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (d, *J* = 5.8 Hz, CH_3CH_2O), 35.4 (d, *J* = 4.0 Hz, CH_2CH), 48.6 (d, *J* = 156.5 Hz, CHP), 55.8 (CH_3O), 55.9 (CH_3O), 62.6 (d, *J* = 6.7 Hz, OCH_2CH_3), 62.8 (d, *J* = 7.1 Hz, OCH_2CH_3), 66.9 (OCH_2Ph), 111.1, 112.2, 121.4, 127.9, 128.1, 128.5, 129.1 (d, *J* = 13.7 Hz), 136.4, 147.9, 148.8, 155.9 (d, *J* = 6.2 Hz, C=O) ppm. ^{31}P NMR (162 MHz, $CDCl_3$, asterisk denotes minor rotamer): δ = 23.59*, 24.21 ppm. HRMS (ESI): calcd. for $C_{22}H_{31}NO_7P$ $[M + H]^+$ 452.1838; found 452.1824.

3-Diethyl (1,2,3,4-tetrahydroisoquinolin-3-yl)phosphonate (7a). Method A: A mixture of compound **5a** (100 mg, 0.39 mmol) in MeOH/H_2O (2.6:1.3 mL), benzotriazole (46.3 mg, 0.39 mmol) and formaldehyde as 37 % aqueous solution (31.5 mg, 30 µL, 0.39 mmol) was stirred at room temperature for 5 h. The clear solution was concentrated, extracted with CH_2Cl_2, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to obtain compound **6** as a colorless oil that was used with no further purification. $ZnBr_2$ (232 mg, 1.03 mmol) was added to a solution of compound **6** (100 mg, 0.26 mmol) in dry dichloromethane (5 mL) in the presence of 4 Å molecular sieves (50 mg), and the resulting mixture was refluxed for 6 h. The reaction mixture was cooled to room temperature, filtered, diluted with dichloromethane (30 mL), washed with 2 M NaOH (20 mL) and brine (10 mL) and dried with anhydrous $MgSO_4$. The solvent was evaporated in vacuo, and the crude product was purified by flash chromatography using AcOEt/MeOH (90:10) to give compound **7a** (48 mg, 70 % yield) as a colorless oil. IR (neat): $\tilde{\nu}$ = 3294, 1240, 1054, 1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 1.35 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 1.92 (br. s, 1 H, NH), 2.88–3.08 (m, 2 H), 3.24–3.33 (m, 1 H), 3.99–4.10 (br. s, 2 H), 4.15–4.24 (m, 4 H, OCH_2CH_3), 6.96–7.03 (m, 1 H, H_{arom}), 7.06–7.17 (m, 3 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (d, *J* = 5.6 Hz, CH_3CH_2O), 28.9, 48.4 (d, *J* = 16.6 Hz), 51.2 (d, *J* = 161.8 Hz), 62.5 (d, *J* = 6.7 Hz, OCH_2CH_3), 62.6 (d, *J* = 6.9 Hz, OCH_2CH_3), 126.2, 126.4, 129.2, 129.2, 133.2 (d, *J* = 14.7 Hz), 135.1 (d, *J* = 1.9 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.16 ppm. HRMS (ESI): calcd. for $C_{13}H_{21}NO_3P$ $[M + H]^+$ 270.1259; found 270.1235. **Method B:** 10 % Pd/C (20 mg) was added to a solution of compound **10a** (100 mg, 0.25 mmol) in ethyl acetate (2.5 mL). The reaction mixture was vigorously stirred under hydrogen for 24 h, filtered, concentrated under reduced pressure, and the crude product was purified by flash chromatography using AcOEt/MeOH (90:10) to afford compound **7a** (66 mg, 99 % yield) as a colorless oil.

Diethyl [2-(Benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-3-yl]phosphonate (10a): $BF_3{\cdot}OEt_2$ (4.35 g, 3.9 mL, 30.7 mmol) was added under argon to a mixture of compound **8a** (4.0 g, 10.2 mmol) and dimethoxymethane (20 mL). The resulting solution was stirred at 35 °C for 12 h. The reaction mixture was diluted with ethyl acetate (40 mL) and water (40 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give compound **10a** (3.5 g, 84 % yield) as a yellow oil. IR (neat): $\tilde{\nu}$ = 1701, 1244, 1052, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, asterisk denotes minor rotamer): δ = 0.91* (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 0.96 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 1.12* (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 1.18 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 3.13–3.33 (m, 2 H), 3.41–3.53* (m, 1 H, OCH_2CH_3), 3.57–3.70 (m, 1 H, OCH_2CH_3), 3.76–4.08 (m, 3 H, OCH_2CH_3), 4.46* (d, *J* = 16.9 Hz, 1 H), 4.53 (d, *J* = 16.7 Hz, 1 H), 4.86–5.08 (m, 2 H), 5.14–5.26 (m, 2 H, OCH_2Ph), 7.01–7.19 (m, 4 H, H_{arom}), 7.28–7.42 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, asterisk denotes minor rotamer): δ = 16.1 (d, *J* = 6.0 Hz, CH_3CH_2O), 16.3 (d, *J* = 6.1 Hz, CH_3CH_2O), 28.3 (d, *J* = 2.3 Hz), 28.5* (d, *J* = 2.2 Hz), 44.4, 46.5 (d, *J* = 154.2 Hz), 47.3* (d, *J* = 154.3 Hz), 61.9* (d, *J* = 6.9 Hz, OCH_2CH_3), 62.1 (d, *J* = 6.9 Hz, OCH_2CH_3), 62.3 (d, *J* = 6.3 Hz, OCH_2CH_3), 67.8 (OCH_2Ph), 67.8* (OCH_2Ph), 125.8, 126.0*, 126.5, 126.5*, 126.6, 128.0, 128.2*, 128.2, 128.5*, 128.6, 128.7, 131.1*, 131.6, 132.6, 132.7*, 136.2*, 136.5, 155.2* (C=O), 155.8 (d, *J* = 2.7 Hz, C=O) ppm. ^{31}P NMR (162 MHz, $CDCl_3$, asterisk denotes minor rotamer): δ = 24.33*, 24.75 ppm. HRMS (ESI): calcd. for $C_{21}H_{27}NO_5P$ $[M + H]^+$ 404.1627; found 404.1608.

Diethyl {(*R*)- and (*S*)-1-[(Benzyloxycarbonyl)amino]-2-phenyl-ethyl}phosphonate (8a): HPLC resolution of racemic *rac*-**8a** was performed using a 250 × 20 mm Chiralpak® IA column and a mixture of *n*-hexane/*i*PrOH (85:15) as eluent at a flow rate of 18 mL/min. The process was monitored by UV absorption at 220 nm. The racemic amino phosphonate **8a** (2.15 g) was dissolved in chloroform (2.7 mL), and 80 µL aliquots of this solution were injected consecutively every 9 min. Each injection was collected into three separate fractions, with equivalent fractions of successive injections being combined. Concentration of the first and third fractions pro-

vided the enantiomerically pure (*R*)-**8a** (1.049 g) and (*S*)-**8a** (1.029 g), both of them as white solids. The second fraction (25 mg) was found to contain a 19:81 mixture of (*R*)-**8a**/(*S*)-**8a**, which was discarded. (*R*)-**8a**: M.p. 63–65 °C, $[\alpha]_D$ = –42.9 (*c* = 1.04, CH_2Cl_2). (*S*)-**8a**: M.p. 63–65 °C. $[\alpha]_D$ = +43.1 (*c* = 1.04, CH_2Cl_2); ref.[29] $[\alpha]_D$ = +42.3 (*c* = 1.05, CH_2Cl_2). Spectroscopic data were identical to those described in the literature.[29]

[(*R*)-1-Amino-2-phenylethyl]phosphonic Acid [(*R*)-11]: Compound (*R*)-**8a** (250 mg, 0.64 mmol) was dissolved in a 33 % solution of HBr in acetic acid (5 mL) and stirred at room temperature for 24 h. The volatiles were evaporated under reduced pressure, and the crude material was purified by ion exchange chromatography on Dowex 50WX8 H^+ form and eluted with water to afford compound (*R*)-**11** (120 mg, 93 %) as a white solid. M.p. 271–272 °C. $[\alpha]_{278}$ = –49.3 (*c* = 0.53, 1 M NaOH); ref.[30] $[\alpha]_{278}$ = –49.9 (*c* = 1.98, 1 M NaOH). Spectroscopic data were identical to those described in the literature.[35]

Diethyl [(*R*)-2-(Benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-3-yl]phosphonate [(*R*)-10a]: Compound (*R*)-**10a** was obtained from (*R*)-**8a** in a way similar to that for *rac*-**10a** as a colorless oil. $[\alpha]_D$ = –4.4 (*c* = 0.50, $CHCl_3$). Spectroscopic data were identical to those described for *rac*-**10a**.

Diethyl [(*S*)-2-(Benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-3-yl]phosphonate [(*S*)-10a]: Compound (*S*)-**10a** was obtained from (*S*)-**8a** in a way similar to that for *rac*-**10a** as a colorless oil. $[\alpha]_D$ = +4.5 (*c* = 0.47, $CHCl_3$). Spectroscopic data were identical to those described for *rac*-**10a**.

[(*R*)-1,2,3,4-Tetrahydroisoquinolin-3-yl]phosphonic Acid [(*R*)-2a]: Compound (*R*)-**10a** (150 mg, 0.37 mmol) was dissolved in a 33 % solution of HBr in acetic acid (2 mL) and stirred at room temperature for 24 h. The volatiles were evaporated under reduced pressure, and the crude material was purified by ion exchange chromatography on Dowex 50WX8 H^+ form and eluted with water to afford compound (*R*)-**2a** (74 mg, 93 %) as a white solid. M.p. 278–280 °C. $[\alpha]_D$ = –103.0 (*c* = 0.42, 1 M NaOH). IR (KBr): $\tilde{\nu}$ = 1215, 1056, 957 cm^{-1}. ^1H NMR (400 MHz, D_2O, K_2CO_3): δ = 3.10–3.25 (m, 3 H), 4.30 (s, 2 H), 7.19–7.32 (m, 4 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, D_2O, K_2CO_3): δ = 28.2, 46.5 (d, *J* = 8.5 Hz), 53.2 (d, *J* = 135.4 Hz), 126.5, 126.6, 127.5, 129.0, 129.8, 133.3 (d, *J* = 11.5 Hz) ppm. ^{31}P NMR (162 MHz, D_2O, K_2CO_3): δ = 12.07 ppm. HRMS (ESI): calcd. for $C_9H_{13}NO_3P$ $[M + H]^+$ 214.0633; found 214.0631.

[(*S*)-1,2,3,4-Tetrahydroisoquinoline-3-yl]phosphonic Acid [(*S*)-2a]: Compound (*S*)-**2a** was obtained in a way similar to that for (*R*)-**2a** in 92 % yield as a white solid. M.p. 278–280 °C. $[\alpha]_D$ = +102.5 (*c* = 0.40, 1 M NaOH). Spectroscopic data were identical to those described for (*R*)-**2a**.

Diethyl {1-[(Benzyloxycarbonyl)(methoxymethyl)amino]-2-(4-bromophenyl)ethyl}phosphonate (14b): BF_3•OEt_2 (182 mg, 0.17 mL, 1.28 mmol) was added under argon to a mixture of compound **8b** (200 mg, 0.42 mmol) and dimethoxymethane (1 mL). The resulting solution was stirred at 35 °C for 36 h. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford compound **14b** (193 mg, 88 % yield) as a yellow oil. IR (neat): $\tilde{\nu}$ = 1710, 1256, 1091, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.31 (m, 6 H, CH_3CH_2O), 2.95–3.27 (m, 5 H, CH_3O, CH_2CH), 3.99–4.17 (m, 5 H), 4.66–5.16 (m, 4 H, CH_2N, OCH_2Ph), 6.96–7.40 (m, 9 H, H_{arom}) ppm. ^{13}C NMR (asterisk denotes minor rotamer, 100 MHz, $CDCl_3$): δ = 16.5 (d, *J* = 5.8 Hz, CH_3CH_2O), 33.6 (CH_2CH), 55.8 (CH_3O), 56.5* (CH_3O), 62.6 (OCH_2CH_3), 62.9* (OCH_2CH_3), 65.4 (d, *J* = 154.4 Hz, CHP), 67.9 (OCH_2Ph), 68.1 (CH_2N), 120.5, 128.1, 128.3, 128.4*, 128.6, 130.9, 131.5, 136.2, 136.7 (d, *J* = 14.9 Hz), 156.4 (C=O) ppm. ^{31}P NMR (asterisk denotes minor rotamer, 162 MHz, $CDCl_3$): δ = 23.51*, 24.03 ppm. HRMS (ESI): calcd. for $C_{22}H_{30}BrNO_6P$ $[M + H]^+$ 514.0994; found 514.0968.

Diethyl {1-[(Benzyloxycarbonyl)(methoxymethyl)amino]-2-[4-(trifluoromethyl)phenyl]ethyl}phosphonate (14c): BF_3•OEt_2 (190 mg, 0.17 mL, 1.34 mmol) was added under argon to a mixture of compound **8c** (200 mg, 0.43 mmol) and dimethoxymethane (1 mL). The resulting solution was stirred at 35 °C for 12 h. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give compound **14c** (195 mg, 89 % yield) as a yellow oil. IR (neat): $\tilde{\nu}$ = 1711, 1257, 1055, 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.30 (m, 6 H, CH_3CH_2O), 2.79–3.43 (m, 5 H, CH_3O, CH_2CH), 3.93–4.25 (m, 5 H, OCH_2CH_3, CHP), 4.65–5.27 (m, 4 H, CH_2N, OCH_2Ph), 7.11–7.54 (m, 9 H, H_{arom}) ppm. ^{13}C NMR (asterisk denotes minor rotamer, 100 MHz, $CDCl_3$): δ = 16.4 (d, *J* = 5.8 Hz, CH_3CH_2O), 16.5* (d, *J* = 5.7 Hz, CH_3CH_2O), 33.9 (CH_2CH), 34.3* (CH_2CH), 55.7 (CH_3O), 56.4* (CH_3O), 62.6 (OCH_2CH_3), 62.9* (OCH_2CH_3), 65.4 (d, *J* = 153.8 Hz, CHP), 67.9 (OCH_2Ph), 68.1 (CH_2N), 124.3 (q, *J* = 271.9 Hz, CF_3), 125.2 (q, *J* = 3.7 Hz), 128.1, 128.3, 128.5*, 128.6, 128.6*, 128.9 (q, *J* = 32.2 Hz), 129.5, 135.8*, 136.1, 141.9 (d, *J* = 15.1 Hz), 156.3 (C=O) ppm. ^{31}P NMR (asterisk denotes minor rotamer, 162 MHz, $CDCl_3$): δ = 23.36*, 23.87 ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –62.37 ppm. HRMS (ESI): calcd. for $C_{23}H_{30}F_3NO_6P$ $[M + H]^+$ 504.1763; found 504.1722.

Diethyl [2-(Benzyloxycarbonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-yl]phosphonate (10d): BF_3•OEt_2 (190 mg, 0.17 mL, 1.34 mmol) was added under argon to a mixture of compound **8d** (200 mg, 0.44 mmol) and dimethoxymethane (5 mL). The resulting solution was stirred at 35 °C for 12 h. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using AcOEt/MeOH (95:5) to provide compound **10d** (128 mg, 64 % yield) as a yellow oil, and the dimeric product **15** (30 mg, 15 % yield) as a yellow oil. **10d:** IR (neat): $\tilde{\nu}$ = 1700, 1259, 1095, 1025 cm^{-1}. ^1H NMR (asterisk denotes minor rotamer, 400 MHz, $CDCl_3$): δ = 0.97* (d, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 1.01 (t, *J* = 6.9 Hz, 3 H, CH_3CH_2O), 1.14* (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 1.19 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 3.01–3.27 (m, 2 H), 3.43–3.57* (m, 1 H, OCH_2CH_3), 3.59–3.73 (m, 1 H, OCH_2CH_3), 3.75–4.09 (m, 3 H, OCH_2CH_3), 3.80 (s, 3 H, CH_3O), 3.83 (s, 3 H, CH_3O), 4.39* (d, *J* = 16.4 Hz, 1 H), 4.46 (d, *J* = 16.3 Hz, 1 H), 4.78–5.08 (m, 2 H), 5.12–5.25 (m, 2 H, OCH_2Ph), 6.52 (s, 1 H, H_{arom}), 6.57* (s, 1 H, H_{arom}), 6.62 (s, 1 H, H_{arom}), 7.27–7.41 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (asterisk denotes minor rotamer, 100 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 5.5 Hz, CH_3CH_2O), 16.4 (d, *J* = 5.6 Hz, CH_3CH_2O), 27.8 (d, *J* = 2.6 Hz), 28.0* (d, *J* = 2.4 Hz), 44.0, 46.5 (d, *J* = 153.9 Hz), 47.2* (d, *J* = 154.1 Hz), 55.9 (CH_3O), 56.0 (CH_3O), 61.9* (d, *J* = 6.9 Hz, OCH_2CH_3), 62.2 (d, *J* = 6.8 Hz, OCH_2CH_3), 62.3 (d, *J* = 6.3 Hz, OCH_2CH_3), 62.4* (d, *J* = 7.2 Hz, OCH_2CH_3), 67.8 (OCH_2Ph), 108.6, 108.8*, 111.1*, 111.3, 122.9*, 123.4, 124.2, 124.5*, 128.1, 128.2, 128.3*, 128.6, 136.2*, 136.5, 147.8, 147.9, 148.0*, 155.2* (C=O), 155.8 (d, *J* = 2.7 Hz, C=O) ppm. ^{31}P NMR (asterisk denotes minor rotamer, 162 MHz, $CDCl_3$): δ = 24.50*, 24.87 ppm. HRMS (ESI): calcd. for $C_{23}H_{31}NO_7P$ $[M + H]^+$ 464.1838; found 464.1814.

Bis(2-{2′-[(benzyloxycarbonyl)amino]-2′-(diethoxyphosphinyl)-ethyl}-4,5-dimethoxyphenyl)methane (15): IR (neat): $\tilde{\nu}$ = 3243,

1718, 1276, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.27 (m, 12 H, CH_3CH_2O), 2.75–2.88 (m, 2 H, $CHCH_2$), 3.05–3.13 (m, 2 H, CH_2CH), 3.69 (s, 6 H, CH_3O), 3.78 (s, 6 H, CH_3O), 3.93–4.15 (m, 10 H), 4.31–4.44 (m, 2 H, CHP), 4.88 (AB system, J = 12.3 Hz, 2 H, OCH_2Ph), 4.99 (AB system, J = 12.3 Hz, 2 H, OCH_2Ph), 5.67 (d, J = 10.1 Hz, 2 H, NH), 6.44 (s, 2 H, H_{arom}), 6.73 (s, 2 H, H_{arom}), 7.13–7.31 (m, 10 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (d, J = 5.9 Hz, CH_3CH_2O), 16.5 (d, J = 5.6 Hz, CH_3CH_2O), 32.2 (d, J = 4.3 Hz, CH_2CH), 35.2 (CH_2), 47.9 (d, J = 155.6 Hz, CHP), 55.9 (CH_3O), 56.0 (CH_3O), 62.6 (d, J = 6.4 Hz, OCH_2CH_3), 62.8 (d, J = 7.2 Hz, OCH_2CH_3), 66.9 (OCH_2Ph), 112.9, 113.3, 127.2 (d, J = 13.8 Hz), 128.0, 128.2, 128.5, 131.2, 136.5, 147.3, 147.7, 156.1 (d, J = 6.0 Hz, C=O) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 24.60 ppm. HRMS (ESI): calcd. for $C_{45}H_{61}N_2O_{14}P_2$ $[M + H]^+$ 915.3598; found 915.3577.

Diethyl (6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-yl)phosphonate (7d). Method A: Formaldehyde (77 mg, 71 µL, 0.95 mmol, 37 % aqueous solution) was added dropwise to a solution of compound **5d** (200 mg, 0.63 mmol) and 2 N HCl (0.32 mL, 0.64 mmol) in EtOH/water (1:0.1 mL). The solution was stirred at room temperature for 32 h. The reaction mixture was concentrated under reduced pressure, diluted with dichloromethane (20 mL), and neutralized with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was separated, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography with CH_2Cl_2/*i*PrOH (90:10) to give **7d** (207 mg, 100 %) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3297, 1244, 1226, 965 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.34 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.89 (br. s, 1 H, NH), 2.76–3.00 (m, 2 H), 3.24 (ddd, J = 15.8, 11.5, 4.5 Hz, 1 H), 3.81 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.96 (s, 2 H), 4.14–4.23 (m, 4 H, OCH_2CH_3), 6.49 (s, 1 H, H_{arom}), 6.57 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (d, J = 5.6 Hz, OCH_2CH_3), 28.4, 48.1 (d, J = 16.8 Hz), 51.2 (d, J = 161.8 Hz), 55.9 (OCH_3), 56.0 (OCH_3), 62.5 (d, J = 6.9 Hz, OCH_2CH_3), 62.6 (d, J = 7.0 Hz, OCH_2CH_3), 109.0, 111.8 (d, J = 1.8 Hz), 125.0 (d, J = 15.2 Hz), 127.0 (d, J = 2.0 Hz), 147.6, 147.7 (d, J = 1.3 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.27 ppm. HRMS (ESI): calcd. for $C_{15}H_{25}NO_5P$ $[M + H]^+$ 330.1470; found 330.1460. **Method B:** Trifluoroacetic acid (1.44 g, 1 mL, 12.63 mmol) was added dropwise to a solution of compound **5d** (200 mg, 0.63 mmol) in dichloromethane (3.2 mL) and formaldehyde (77 mg, 71 µL, 0.95 mmol, 37 % aqueous solution) at room temperature. The solution was stirred at room temperature for 5 h. Then, the workup was identically to that before to obtain **7d** in quantitative yield as a yellow oil.

(6,7-Dihydroxy-1,2,3,4-tetrahydroisoquinolin-3-yl)phosphonic Acid (2d): Compound **7d** (400 mg, 1.2 mmol) was dissolved in 48 % HBr (5 mL) and refluxed for 3 h. The volatiles were evaporated under reduced pressure, and the product was precipitated from water to afford **2d** (242 mg, 81 %) as a white solid. M.p. 275–277 °C. IR (neat): $\tilde{\nu}$ = 3175, 1284, 1133 cm^{-1}. ^1H NMR (400 MHz, D_2O, K_2CO_3): δ = 2.97–3.10 (m, 2 H), 3.18–3.28 (m, 1 H), 4.22 (s, 2 H), 6.64 (s, 1 H, H_{arom}), 6.73 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, D_2O, K_2CO_3): δ = 26.8, 45.4 (d, J = 6.7 Hz), 53.2 (d, J = 132.0 Hz), 113.4, 115.6, 119.2, 124.1 (d, J = 11.1 Hz), 143.4, 144.4 ppm. ^{31}P NMR (162 MHz, D_2O, K_2CO_3): δ = 9.99 ppm. HRMS (ESI): calcd. for $C_9H_{13}NO_5P$ $[M + H]^+$ 246.0531; found 246.0527.

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